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Fragmentation of Nitrone Triflates to 9-Membered Rings

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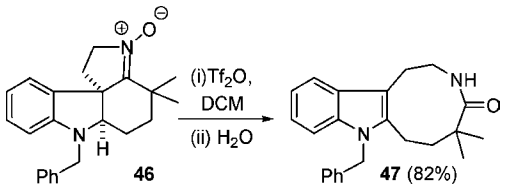
ABSTRACT

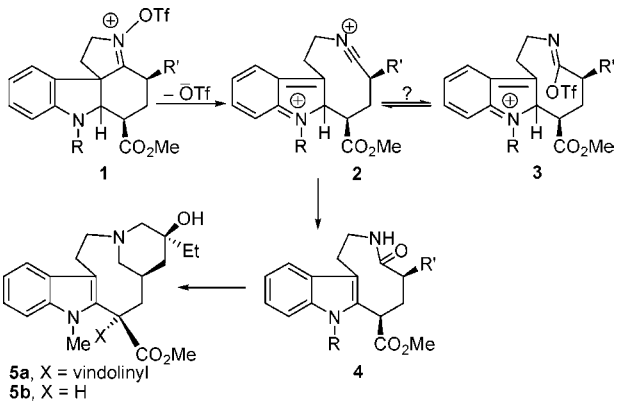


A new fragmentative rearrangement of nitrone derivatives to form 9-membered rings is reported. The fragmentations are triggered when nitrones are treated with triflic anhydride; a C–C bond antiperiplanar to the cleaving N–O bond is activated either by an oxygen lone pair or by an electron-rich aromatic ring. In the former case, further cyclization of the 9-membered intermediate leads to a rearranged condensed ring system, but when triggered by arenes, 9-membered ring amides are isolated.

Medium-sized rings are difficult to form by cyclization processes, due to the inherent strains in the transition state leading to formation of the ring and due to the entropic difficulty of forming such rings from acyclic precursors. For this reason, new routes to medium-sized rings are frequently sought.[1] The research undertaken in this paper was based upon a new potential route to generate medium-sized rings using rearrangements of nitrone triflates. The possibility of using the fragmentation of an activated nitrone such as a nitrone sulfonate **1**, in approaches to the anti-tumor agent, vinblastine **5** (X = vindolinyl) is attractive, since this would afford the product **4** with an amide in a 9-membered ring, ripe for further elaboration toward vinblastine **5a** or carbomethoxyvelbanamine **5b** (Scheme 1).

Whereas rearragements of nitrones are known, they do not include this type of fragmentative process. Thus, a number of groups have studied[2] rearrangements of sulfonylated nitrones. Barton had shown[2a] that tosylation of nitrones derived from steroidal ketones gave product **6** that underwent a migratory rearrangement to **9** that superficially resembled a Beckmann rearrangement (Scheme 2), forming a new C−N σ-bond in the process. However, in contrast to the Beckmann reaction, both (*Z*)- and (*E*)-nitrone derivatives **6** afforded the

Scheme 1



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(1) (a) Shiina, I. *Chem. Rev.* **2007**, *107*, 239. (b) Illuminati, G. G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.

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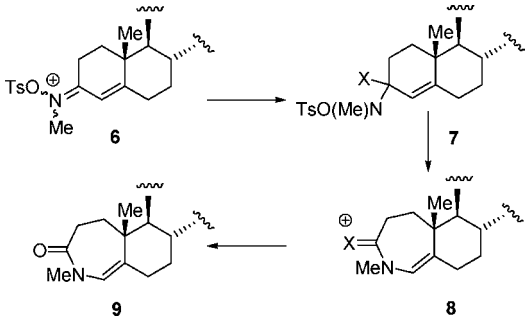
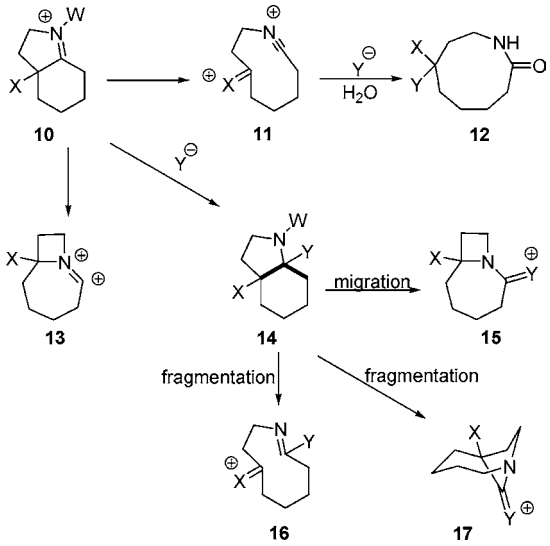
Scheme 2



identical product **9**. This was attributed to the migration occurring via a tetrahedral adduct of type **7**, and possibly being triggered during aqueous workup (i.e., X = OH).

We proposed to test for an alternative and previously unobserved reaction in which ring-fragmentation to a macrocycle would occur. If such a fragmentation could be found, it might subsequently be applied to synthesis of the 9-membered ring of vinca alkaloids, like vinblastine **5a** through rearrangement of compound **1** or analogues, where electron release from the indoline might trigger the fragmentation. We now report the first examples of such a fragmentative rearrangement in this challenging setting of formation of 9-membered rings and examine the parameters where an electron-rich aromatic ring or the lone pair of an oxygen atom (X in structure **10**, Scheme 3) are used to provide the source of electronic push.

Scheme 3

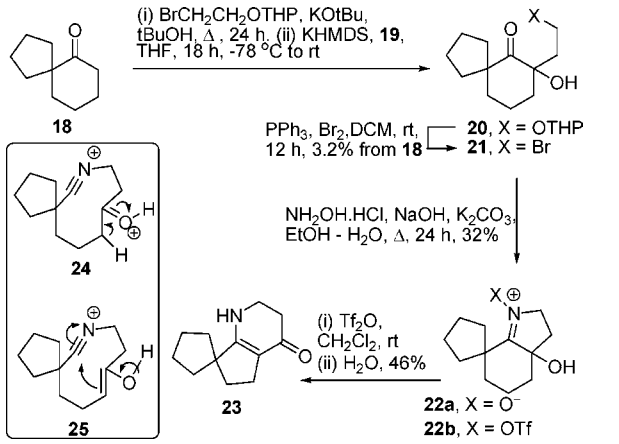


The processes under consideration are shown in Scheme 3. First, if reaction arises from loss of the leaving group W in **10**, a concerted Beckmann-type process giving rise to the very unstable vicinal dication **13** as an intermediate looks very unattractive. On the other hand, formation of a 9-membered ring **11**, driven by an electron-releasing X-group, would afford macrocyclic amide **12** as product.

The alternative possibility, where reaction arises from an adduct **14**, features three processes that break C−C bonds, one driven by electron-release from X, to afford **16**, and two driven by Y, to afford **15** and **17** respectively. The formation of **16** depends on X being a much more effective electron-pair donor than Y.

For our studies, we chose nitrone triflates, where W = Y = OTf. With the known properties of the triflate anion as an outstanding leaving group and as a very poor nucleophile, the addition to molecule **10** to form **14** (analogous to that proposed by Barton in conversion of **6** to **7**) is made less likely, while using triflate as the leaving group (W) in **10** maximizes the chance of fragmentation of **10** to **11**. This fragmentation should also benefit from stereoelectronic advantages, as seen in the conversion of **1** to **2**, where the inter-ring bond that is targeted for cleavage is antiperiplanar to the leaving group, assisting with the selectivity and mildness of the reaction. Such stereoelectronic advantages would apply optimally to functionalized nitrones (sp^2 nitrogen), as here, rather than to amine derivatives (sp^3 nitrogen) bearing a leaving group. Nevertheless, the fragmentation reaction to form the 9-membered ring might also occur from adduct **14**. Here the inter-ring bond targeted for cleavage and the N−OTf bond have partial, but not optimal, overlap. In terms of substrate design, such adduct formation could be further discouraged by choosing ketone-derived nitrones that are hindered on the α and α′-carbons.

Scheme 4



The first substrate, **22a**, was prepared as in Scheme 4. Alkylation of the known spirocyclohexanone **18** followed by hydroxylation with 2-benzenesulfonyl-3-phenyloxaziridine **19**[3] led to alcohol **20**, which was converted directly to

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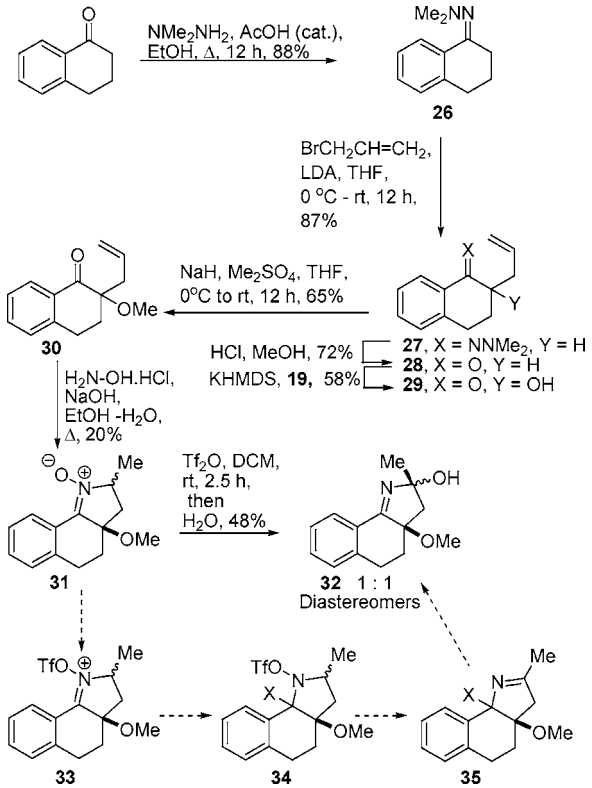
(3) (a) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241. (b) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703.

bromide **21** which, on treatment with hydroxylamine, afforded nitrone **22a**. Reaction with triflic anhydride led to a single new rearranged product, **23**, in 46% yield. This product must arise by forming the nitrone triflate **22b** as desired. Loss of triflate anion and activation by the hydroxyl group lone pair then cause ring-expansion to 9-membered ring-containing intermediate **24**. Clearly, this compound is highly reactive and undergoes formation of enol **25**, cyclization and tautomerism to give observed product **23**.

The formation of **23** happily shows that substrate **22** does not follow the type of rearrangement observed by Barton et al.,[2a] but instead proceeds by the desired fragmentation.

As mentioned above, the fragmentation reactions could occur either directly from the nitrone triflates or from their triflate adducts. In one substrate, nitrone **31**, we saw possible evidence of the intermediacy of an adduct. However, that adduct led to an anomalous outcome. The synthetic route to nitrone **31** is depicted in Scheme 5. α-Tetralone was

Scheme 5



converted into its hydrazone derivative **26** in 88% yield by treatment with *N*,*N*-dimethylhydrazine in the presence of a catalytic amount of acetic acid. Allylation with LDA and allyl bromide gave product **27** in 87% yield. Hydrolysis of the hydrazone proceeded smoothly to provide the allylated ketone **28** in 72% yield, treatment of which with Davis' oxaziridine[3] **19** provided the hydroxyketone **29** in 58% yield. The hydroxyketone was converted into its methyl ether **30** in good yield.

Treatment of ether **30** with hydroxylamine hydrochloride gave the desired nitrone **31**[4] as a diastereomeric mixture (ratio 2:1), which was separated by column chromatography.

The nitrone **31** (major isomer) was exposed to triflic anhydride. In this case, a completely unexpected type of rearranged product was obtained as an inseparable mixture of diastereomers **32** (dr 1:1 from NMR) in 48% yield (Scheme 5). The formation of the products **32** was confirmed by spectroscopy and, following crystallization, by X-ray crystallography.

A proposal for the formation of the rearranged product **32** is shown in Scheme 5. The nitrone **31** is transformed to a reactive nitrone triflate **33**. Attack by external nucleophile X^- to form **34** (or 3-membered ring formation by the adjacent methoxy group behaving as an intramolecular nucleophile) would permit loss of triflic acid (by a *syn*- or *anti*-elimination) to afford the imine **35**. Addition of nucleophile H_2O on workup, followed by loss of X^- then produces the isolated conjugated products **32**. Why does nitrone **31** behave in this anomalous way? Given the contrast with nitrone **22a**, the difference may be associated with the fused aromatic ring. Certainly, the planarity of the aryl ring can facilitate nucleophilic attack on the nitrone C═N bond. Formation of the adduct can also ease crowding around the triflate group in this case.

The models that had been employed so far had used the lone-pair of an oxygen directly bonded to the carbon α- to the nitrone to trigger the fragmentation. We were more interested to explore whether an electron-rich arene could also drive this type of fragmentation.

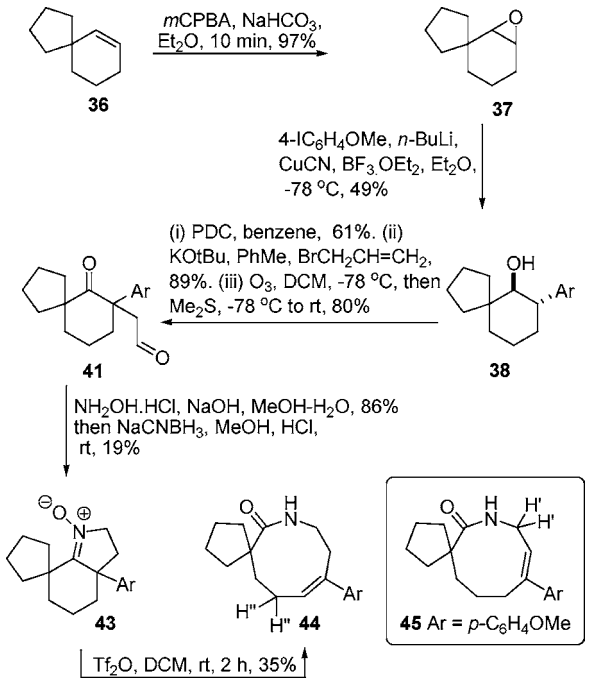
The synthetic strategy designed for the synthesis of model nitrone **43** is shown in Scheme 6. The alkene **36** was epoxidized with *m*-CPBA to provide the epoxide **37** in 97% yield. Subsequent ring-opening with an organocuprate derived from 4-iodoanisole gave the alcohol **38** in 49% yield.

Oxidation with PDC in refluxing benzene afforded ketone **39**, which was allylated using allyl bromide and KO^{t}Bu. The allylated product **40** was formed in 89% yield. Ozonolysis of **40** afforded aldehyde **41**. Treatment with hydroxylamine hydrochloride and NaOH gave the aldoxime **42** as a pair of diastereomers in good yield. This was then reduced using $NaCNBH_3$ in the presence of methanolic HCl (pH 3) to give the desired nitrone **43** in 19% yield from **41**.

The successful formation of nitrone **43** led to an attempt at ring fragmentation reaction. Thus, **43** was first exposed to triflic anhydride, and then treated with water (Scheme 6). It was heartening to see that the desired ring-expanded product **44** was formed in 35% yield as a pair of diastereoisomers, resulting from geometric isomerism about the alkene or, possibly, about the amide. It was clear that the product was regioisomer **44** rather than **45** from 2D ^{1}H,^{13}C HSQC and 2D ^{1}H,^{1}H COSY spectra. Thus, from the ^{1}H NMR spectrum, the vinyl protons resonating at δ 5.15−5.20 and δ 5.25−5.27 ppm (correlating respectively with ^{13}C signals

(4) We see this as likely resulting from oxime formation followed by retro-Cope reaction. (a) Grigg, R.; Heaney, F.; Markandu, J.; Surendakumar, S.; Thornton-Pett, M.; Warnock, W. J. *Tetrahedron Lett.* **1991**, *47*, 4007. (b) Gravestock, M. B.; Knight, D. W.; Thornton, S. R. *J. Chem. Soc., Chem. Commun.* **1993**, 169.

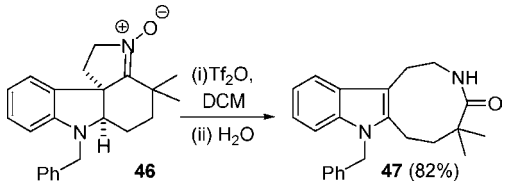
Scheme 6



at δ 119.5 and δ 123.8 ppm), both coupled with protons H″ in the range δ 1.8−2.3 ppm. By contrast, if **45** had been produced, the vinyl proton would couple to protons H′, which are expected to resonate considerably downfield of this value.

We then focused on the synthesis of the key indoline nitrone **46**; this was available by the approach of Gramain et al.[5] Initially, the rearrangement reaction of **46** did not proceed in high yield, but this example was crucial to our future plans, and so we engaged in extensive optimization studies. Happily, these steadily improved matters until an easily repeatable 82% of indole **47** was obtained, providing a launchpad for the exploration of more complex substrates (Scheme 7).

Scheme 7



In summary, we have reported the first examples of fragmentative rearrangements of nitrone triflates, and have focused on fragmentations that lead to 9-membered rings. The application to the synthesis of the fused indole **47** complements the more widely used alkaloid rearrangements of tertiary amine oxides,[6] and opens a new avenue for the preparation of stable macrocyclic amides.

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Supporting Information Available: Experimental procedures and spectra for obtained compounds; X-ray data for **32** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL071049D

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